REMARKS/ARGUMENTS

A. **General:**

1. Claim 7 has been amended to correct a typographical error.
2. Claims 1-11 remain in the application.

B. **Information Disclosure Statement:**

Applicants thank the Examiner for the reminder of the need for a separate Information Disclosure Statement which Applicants are submitting with this amendment.

C. **Drawings Objection:**

The Examiner has objected to the drawings for failing to comply with 37 CFR 1.84 (p)(4) because reference character "104" has been used to designate both concentrator and inlet. The Examiner states that Figs. 1 and 2 should be designated by a legend such as -- Prior Art -- citing MPEP §608.02(g).

Applicants have added the legend, -- Prior Art --, to Figs. 1, 1a, 2, 2a, and 2b and have renumbered the Concentrator in Fig. 3 to -- 105 -- to eliminate the duplicate reference to 104 which is also used to designate the inlet. Applicants have also amended paragraph [0044] of the specification to reflect this change. Applicants submit that the above amendments obviate the Examiner's objections to the drawings.

D. **Claim Objection:**

The Examiner has objected to claim 7 because of an informality, i.e., a typographical error.

Applicants have amended claim 7 to correct the error thereby obviating this objection.

E. **102 Rejection:**

The Examiner has rejected claims 1-10 under 35 USC 102(e) as being anticipated by Schulist et al. (6,229,842).

1. With regard to the Examiner's rejection of claims 1, 2, and 10, Applicants' application of CFAR together with their adaptive noise estimate are novel in the recited use in conjunction with mass spectrometry. Schulist et al., on the other hand, applies their version of "CFAR" to finding an optimum electromagnetic signal propagation path. Not once is mass spectrometry mentioned.

Applicants' invention is novel and not anticipated by Schulist et al. because the Schulist technique does not address factors relevant to the time-of-flight mass spectrum, and as such would not work with a mass spectrum; and Schulist's "CFAR" does not disclose crucial elements of noise estimation, which Applicants' technique provides. To explain further:

a. Schulist, in addressing an electromagnetic spectrum, does not consider the non-linear relationship between time and mass-to-charge ratio (m/z) in a mass spectrum (non-electromagnetic spectrum). Thus, their spectral bins would not properly account for mass bin widths in a mass spectrum, derived from uniform time sampling of a molecular ion detector. These bin widths are essential for determining a single resolution cell of a mass spectrometer, and thus for determining how many time samples constitute a valid signal. This in turn is a prerequisite for determining SNR and threshold setting when detecting peaks in mass spectra. Furthermore, in a matrix-assisted-laser desorption (MALDI) mass spectrum there are peaks associated with the chemical matrix. Schulist's method makes no provision for matrix peaks, and so would confuse them with signal peaks or consign them to "noise" and so corrupt the noise estimate.

b. Schulist's implementation of "CFAR" addresses their particular concerns with electromagnetic propagation path selection. It is inappropriate for a mass spectrum with its radically shifting baseline, plethora of irrelevant peaks, and variability of noise statistics. It certainly would not guarantee a constant false alarm rate when processing mass spectra background data. Schulist's threshold calculation is predicated on SNR, which also is completely useless for MALDI mass spectra because of the presence of irrelevant peaks with arbitrarily high signal levels. Applicants' invention as described and

claimed is an approach suited to mass spectra, wherein an appropriate background noise statistics model can be selected from the mass spectrometer set-up data (no signal-producing chemicals present), then used in conjunction with a split window normalizer to adaptively estimate the parameters of the noise statistics model. Applicants' threshold is based on adaptively inverting the statistical model (parameters having been estimated) to produce a threshold value that will ensure a constant false alarm rate, to the accuracy that the statistical model represents the test data. The accuracy of this approach in producing a true constant false alarm rate has been verified in many trials of the system. Peaks are then easily identified as excursions beyond this threshold. Neither the concept of a parametric statistical model nor the split window normalizer implemented to traverse the spectrum from high to low masses in Applicants' application are mentioned anywhere in Schulist et al.

2. With regard to the Examiner's rejection of claim 3, again, Schulist discloses a procedure for processing spread spectrum electromagnetic spectra, not molecular time-of-flight mass spectra. A few of the differences are described in response to the rejection of claims 1, 2, and 10. Also as discussed above, Applicants' CFAR technique differs fundamentally, down to the enabling equations, from the Schulist "CFAR." Beyond this, Applicants' method identifies peaks that may contaminate the noise estimate, based on Applicants' analytical model of the noise. The time samples containing these peaks are replaced with draws from the analytical noise model to update Applicants' noise estimate as the estimator is advanced to higher values of m/z. Nowhere is the concept of sample replacement from an analytical noise distribution, nor moving the noise estimator from low to high portions of the spectrum disclosed in Schulist et al.

3. With regard to the Examiner's rejection of claim 4, the only "succession" that Schulist et al. describe is an iterative method for removing peaks en-masse from an electromagnetic-related spectrum and re-calculating the noise estimate. There is no disclosure of "resolution" in the cited portion of Schulist's patent, and in particular no addressing of the variable time resolution of a mass spectrometer, since Schulist addresses only electromagnetic, not time-of-flight mass, spectra. Applicants' technique

explicitly calculates the mass spectrum signal cell size in terms of time samples at each step through the mass spectrum time series. There is no analog in the electromagnetic spectra Schulist treats.

4. With regard to the Examiner's rejection of claim 5, since Schulist et al. doesn't work with mass spectrum data, they don't claim to compare it to a threshold. Applicants submit that Schulist's comparing any estimate to a noise-derived threshold and deciding "signal present" if the estimate exceeds the threshold is simply general practice in the signal processing art and not Applicants' invention.

5. With regard to the Examiner's rejection of claim 6, in the column and line numbers cited by the Examiner, Schulist et al. describe their procedure for removing peaks and calculating the mean residual noise. Applicants' procedure, in the mass spectral domain, is a generalization of Schulist et al. While Schulist et al. calculates only the mean, Applicants calculate the maximum likelihood estimate of the parameters of Applicants' analytical statistical model of the noise. For a Gaussian noise model, this means finding the mean and standard deviation. For a gamma noise model, this means calculating gamma distribution parameters "a" and "b," neither of which is a "mean." The parameters Applicants estimate depend on the noise model appropriate for the mass spectrometer being used for the measurement.

6. With regard to the Examiner's rejection of claim 7, as described above, Schulist's method for attempting to achieve constant false alarm rate is quite different from Applicants' and would not achieve a constant false alarm rate with a mass spectrum (and therefore could not be called a CFAR). So while both Applicants' method and Schulist's use a noise estimate in a sample cell, the similarity ends there. The cited column and line numbers in the Examiner's rejection of claim 7 neither mention the need in a mass spectrum split window normalizer to update the noise estimate as the normalizer advances from low mass to high mass, nor any technique for doing so. These are described in full detail in Applicants' application.

7. With regard to the Examiner's rejection of claim 8, because Schulist's application is identification of an optimum propagation channel, there is no "threat." In mass spectrum processing the "threat" is a release of a hostile virus or bacteria such as anthrax. Schulist's sole criterion for selecting a peak is that it provides the best communication link. There is no database of peaks to which he compares his optimum propagation path peak. Applicants, on the other hand, do disclose and claim a data base of virus and bacteria mass spectrum peaks. Applicants' invention must compare all peaks detected with a library of signatures of pathogens to service the need of the mass spectrometer user. The column and line numbers cited by the Examiner in Schulist's patent are not relevant to identifying any threat, much less one of the complicated nature of a mass spectrum signature. Applicants' invention addresses this need.

8. With regard to the Examiner's rejection of claim 9, to reiterate and expand on the previous response above: Schulist et al. rank their peaks to select an optimum- the best peak indicating the best communication. This is a completely different problem than in mass spectrum processing. There is no "optimum" mass spectrum peak. There is no best amplitude of a mass spectral peak. Mass spectra peaks must be considered *in groups* and linked *by group* to a library of signatures with the same sequence of peaks (same m/z values), in a similar vein to matching of fingerprints. Because this is completely different, Schulist's peak ranking is totally inappropriate and not useful for mass spectrum processing. Applicants' invention addresses this need.

For all the reasons discussed above, Schulist et al. does not anticipate claims 1-10.

F. **103 Rejection:**

The Examiner has rejected claim 11 under 35 USC 103(a) as being unpatentable over Schulist et al.

For all the reasons discussed above why claims 1 and 10 are not anticipated by Schulist et al., Schulist et al. cannot render obvious claim 11.

G. **Conclusion:**

In view of the above, Applicants submit that each of the presently pending claims in this application is in immediate condition for allowance. Reconsideration and withdrawal of the objections and rejections are requested. Allowance of claims 1-11 at an early date is solicited.

Respectfully submitted,

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Attachments:
Replacement Sheets for Figs. 1, 1a, 2, 2a, 2b, and 3
Annotated Sheets Showing Changes to Figs. 1, 1a, 2, 2a, 2b, and 3
Information Disclosure Statement with 5 references